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Short communication

Tolerance of BNT162b2 mRNA COVI-19 vaccine in patients with a medical history of COVID-19 disease: A case control study

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ABSTRACT

Introduction: Studies evaluating BNT162b2 mRNA Covid-19 vaccine safety excluded subjects with a previous history of COVID-19 infection. The aim of our study was to focus on the tolerance of this vaccine this population.
Methods: An anonymous self-reporting survey related to safety and tolerance of vaccine was completed by subjects 21 to 28 days after the first vaccine dose in two vaccination centers.
Results: Subjects with prior COVID-19 disease history (n = 61) had higher systemic reactions than subjects without any previous history (n = 1987) (45.9% vs 29.7%, p = 0.01). Asthenia, headache and fever were significantly more frequent in COVID-19 + group than negative group (25.6% vs 15.2% p = 0.045, 19.7% vs 9.3% p = 0.01, 6.5% vs 0.9% p = 0.003 respectively). Grade of severity was higher in COVID-19 + than in COVID-19 - group (p = 0.03).
Conclusion: Our study confirms a higher risk of side effects in patients with preexisting SARS-CoV-2 disease but with a good overall tolerance.

1. Introduction

As of March 24, 2021, a total of 4.378.448 cases of coronavirus disease 2019 (COVID-19) and 93.180 associated related deaths have been reported in France [1] On the 21th of December 2020, the European Medical Agency approved vaccination to prevent COVID-19 with Pfizer-BioNTech COVID-19 vaccine, administered as 2 doses separated by 21 days. In France initial doses were recommended for health care professional with risk factors of severe COVID-19 disease, long-term care facility residents and was extended to people with high risk to develop severe COVID-19 disease (>75 years, immunosuppression treatment for cancer, solid organ transplant, allograft, or auto-immune disease) [2] Since the 11th of February 2021, according to the French Health Authority, people with a medical history of COVID-19 disease should receive only one (mRNA or adenovirus-vectored) vaccine dose except if they are immunocompromised (2 doses of vaccine) [3] Vaccine should not be given earlier than 3 months after the infection. [3] BNT162b2 mRNA Covid-19 vaccine is generally well tolerated with a low rate of serious adverse events in patients with no medical history of COVID-19 [4] Studies evaluating vaccine efficacy and safety excluded patients with a previous history of COVID-19 infection, thus few information are available on vaccine safety in this population.[4,5]

The objective of this study is to compare the tolerance of the first shot of BNT162b2 mRNA COVID-19 vaccine between subjects with and without history of previous SARS-CoV-2 infection.

2. Material and Methods

2.1. Study design and setting

An anonymous self-reporting survey related to safety and tolerance of BNT162b2 mRNA Covid-19 vaccine was developed for this study based on the Severity Grading Criteria for Select Physical Observations (Based Center for Biologics Evaluation and Research Grading Table) used by *Polak et al.* in their study.[4,6] All patients who received the first dose of BNT162b2 mRNA Covid-19 vaccine

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between the 06/01/2021 and the 10/02/2021 in the vaccination centers of University Hospital of Caen and Misericorde Foundation Center, France were proposed to complete the survey when they came for the second shot, 21 to 28 days after the first dose.

2.2. Data collection and definitions

This survey was used to collect information regarding demographic characteristics (sex, age), characteristics and date of prior COVID-19 disease, post vaccine symptoms (severity and duration). Patients were considered to have a medical history of COVID-19 disease if they had a documented preexisting SARS-Cov-2 infection (serology or PCR). Local reaction was defined as local pain or local eruption on site of the vaccine injection. Systemic reaction was defined as all others symptoms than those included in the definition of local reaction such as fever, headache, myalgia, gastro intestinal symptoms, pulmonary symptoms, neurological symptoms, chills, general rash, arthralgia, asthenia, adenitis. Patients can develop local and/or systemic reaction.

2.3. Statistical analysis

No sample size computation was performed and we included all consecutive data available. We compared the side effects, the number of side effects, the sum of the side effect grades and the worst side effect grade among subjects with (case) and without (control) prior COVID-19 infection using Student *t*-test for independent samples in the overall cohort or Fischer test when appropriate. In addition, we matched 3 to 12 controls based on age and sex for each case. In the matched analysis, the comparison of the number of side effects, sum of the grades and mean of the worst grade the number of side effects, the sum of the side effect grades and the worst side effect grade among cases and control was performed by generalized linear model with exchangeable correlation structure, to take into account the correlation within each matched cluster. Continuous variables were expressed as means, and categorical variables were reported as percentages. The analyses were done with SAS V9.4 (SAS institute, Cary, NC) and a p-value < 0.05 was used to denote statistical significance. This study was approved by the ethics committee of Caen Hospital (ID 2202) and was performed in accordance with the Declaration of Helsinki.

3. Results

3.1. Characteristics of population

During the inclusion period, 2048 subjects completed the survey prospectively. Median age was 60 years (18–100) and 60.7% were female. 42.3% (n = 867) of population had no side effect after the first dose while 46% (n = 943) had a local reaction,30.1% (n = 618) a systemic reaction among which 380 subjects had both local and systemic reaction. The most frequent systemic side effects were asthenia (15.5%), myalgia (12.7%) and headache (9.6%) (Table 1). Symptoms generally resolved within 3 days and only 192 subjects (9.3%) reported a side effect higher than grade 1. On the 1181 subjects with an adverse events, only one reported the side effect to the national pharmacovigilance system.

3.2. Comparison of tolerance of vaccine in COVID-19 + group versus COVID-19 – Group in overall cohort

61 patients had a medical history of COVID-19 infection; 37 (60.6%) were female with a mean age of 61.4 years old (35–89). 52 patients had a symptomatic COVID-19 infection with only one severe infection requiring hospitalization. Median duration of symptoms was 10 days (2–300) and infection occurred for 20 patients (32.8%) in the last six months prior vaccination. Some patients reported COVID-like symptoms after de vaccine shot, but these where nonspecific and mimicked flue like illness. The time between illness (<or > 6 months) and vaccination did not affect the occurrence (76.2% for COVID-19 < 6 months group vs 73.2% for COVID-19 > 6 months group, p = 0.99) or severity of side effect (mean of grade 0.92 for COVID-19 < 6 months group vs 0.86 for COVID-19 > 6 months group, p = 0.7).

COVID-19 + and COVID-19 – group were comparable for age and sex (Table 1). Regarding all side effects, COVID-19 + group had significant higher rate of systemic reaction post vaccine than COVID-19 - group (45.9% vs 29.7%, p = 0.01) while they had significant lower rate of absence of side effect than COVID-19 - group (26.2% vs 42.8%, p = 0.01). Asthenia, headache and fever were significantly more frequent in COVID-19 + group than in COVID-19 - group (25.6% vs 15.2% p = 0.045, 19.7% vs 9.3% p = 0.01, 6.5% vs 0.9% p = 0.003 respectively). The mean severity and duration of these 3 systemic symptoms were not different between the two groups (Table 1). However, participants with a history of COVID-19 had higher peak side effect (p = 0.03) and sum of grade of side effects (1.75 vs 1.14, p = 0.006) level than COVID-19 patients. Number of side effect was also higher in COVID-19 + group as compared to the COVID-19 – group (1.45 vs 0.96p = 0.0016).

3.3. Comparison of tolerance of vaccine in COVID-19 + group versus COVID-19 – Group in the matched population.

As reported for the whole population, side effect were significantly more frequent in the COVID-19 + group than in the COVID-19 – matched group for age and sex (1.46 vs 1.04, p = 0.02). Severity of side effect was also significantly higher in the COVID 19 + group (Table 2).

4. Discussion

We report new results on the tolerance profile of the first injection of the BNT162b2 mRNA COVID-19 vaccine on a large cohort of >2000 patients. A third of subjects reported a systemic reaction with low severity grade which generally resolved within 3 days. Compared to the population of>55 years of *Polack et al.* study's ours was slightly older (62 mean years old) and included more women (60,7 vs 49.4%).[4] Tolerance observed in our study was good with fewer systemic side effects and fewer local reaction. This could be due to an older age as previous report showed poorer tolerance of mRNA vaccines in younger subjects.[4,5] On the 11th of March 2021, 5.372.206 doses of the BNT162b2 mRNA COVID-19 vaccine were administrated in France. With 9841 cases of adverse events potentially caused by the vaccine reported to the French system of pharmacovigilance, the declaration rate was of 0.18%.[7] Of these: 78.3% were non severe and 21.7% were severe. In our study, although 192 (9.2%) patients presented a grade 2 or 3 adverse event, only one reported a side effect (post vaccine herpes infection) to the pharmacovigilance department. Thus, French pharmacovigilance system probably underestimates side effects frequency because of a low rate of declaration.

We share new data on tolerance in patients with a previous history of COVID-19 infection. The local reaction was similar but we observed more frequent systemic side effects with a higher severity grade in patients with a previous COVID-19 infection. None of these side effects required hospitalization and they usually resolved within a few days. *Krammer and co* have found that a single dose of mRNA vaccine resulted in a higher frequency of side effects in COVID-19 seropositive patients compared to seronega-

Table 1
Tolerance of vaccine in overall population and COVID-19 + versus COVID-19 - groups

	COVID-19 + (n=61)	COVID-19 - (n=1987)	p	Total (n=2048)
Age (mean years old)	61.4	62.2	0.6	62
Female n (%)	37 (60.6)	1206 (60.7)	0.99	1243 (60.7)
Side effects n (%)				
No side effect	16 (26.2)	851 (42.8)	0.01*	867 (42.3)
Local reaction	33 (54.1)	910 (45.8)	0.2	943 (46)
Systemic reaction	28 (45.9)	590 (29.7)	0.01*	618 (30.1)
Asthenia n (%)	15 (25.6)	302 (15.2)	0.045*	317 (15.5)
Grade (mean)	1.33	1.25	0.54	
Duration (mean days)	1.66	2.8	0.37	
Headache n (%)	12 (19.7)	184 (9.3)	0.01*	196 (9.6)
Grade (mean)	1.25	1.22	0.84	
Duration (mean days)	1.5	2.54	0.5	
Chills n (%)	6 (9.8)	56 (2.8)	0.009	62 (3)
Myalgia n (%)	4 (6.5)	257 (12.9)	0.17	261 (12.7)
Abdominal pain n (%)	1 (1.6)	29 (1.4)	0.59	30 (1.5)
Arthralgia n (%)	2 (3.3)	65 (3.3)	1	67 (3.3)
Paresthesia n (%)	1 (1.6)	38 (1.6)	1	39 (1.9)
Thoracic pain n (%)	1 (1.6)	16 (0.8)	0.4	17 (0.8)
Dyspnea n (%)	1 (1.6)	13 (0.6)	0.34	14 (0.7)
Fever n (%)	4 (6.5)	18 (0.9)	0.003*	22 (1)
Grade (mean)	1.50	1.11	0.16	
Duration (mean days)	1.50	1.66	0.89	
Vomiting n (%)	0 (0)	2 (0.1)	0.99	2 (0.09)
Cutaneous reaction n (%)	1 (1.6)	7 (0.3)	0.2	8 (0.4)
Diarrhea n (%)	0 (0)	9 (0.4)	0.99	9 (0.4)
Anosmia/Ageusia n (%)	0 (0)	5 (0.2)	0.99	5 (0.2)
Local adenitis n (%)	1 (1.6)	4 (0.2)	0.1	5 (0.2)
Herpes n (%)	1 (1.6)	1 (0.05)	0.058	2 (0.09)
Dizziness n (%)	0 (0)	2 (0.1)	0.99	2 (0.09)
Grade of side effect n (%)				
Grade 0	16 (26.2)	851 (42.8)		867 (41.3)
Grade 1	36 (59)	953 (48)	0.03*	989 (48.3)
Grade 2	8 (13.1)	159 (8)		167 (8.1)
Grade 3	1 (1.6)	24 (1.2)		25 (1.2)
Number of side effects (mean)	1.45	0.96	0.0016*	0.98
Sum of grade of side effects (mean)	1.75	1.14	0.006*	1.16

*p<0.05.

Table 2
Tolerance of vaccine in the match population

	COVID-19 + (n=61)	COVID-19 - (n=450)	p
Age (mean years old)	61.8	61.7	0.99
Female n (%)	38 (62)	281 (62)	1
Number of side effects (mean +/- SD)	1.46 +/- 1.4	1.04 +/- 1.35	0.02*
Sum of grade of side effects (mean +- SD)	1.76 +/- 1.26	1.25 +/- 1.08	0.03*
Grade of side effects (mean +/- SD)	0.9 +/- 0.68	0.7 +/- 0.68	0.03*

*p<0.05.

tive patients (89% vs 46% respectively) with higher difference than in our study (73.8% vs 57.2% respectively).[8]

However their control group included only 148 patients and it was not mentioned if the two group were adjusted for age or sex. Fatigue and headache were also the main systemic adverse event in their study. No data were available on reported symptoms and date of the infection in *Krammer et al* study.[8] In our work time between illness (<or > 6 months) and vaccination did not affect the occurrence or severity of side effects but the COVID19 + group was small. Unfortunately we did not record the intensity of COVID-19 symptoms in the survey. However only one patient had a severe COVID-19 infection (defined as: requiring oxygen, hospitalization in a COVID-19 department or in intensive care unit). Therefore, we were unable to analyze the correlation between symptom severity or severe COVID19 infection with reactogenicity after vaccination.Few studies have reported significantly higher antibody titers in subjects with a previous COVID-19 infection vaccinated with BNT162b2 mRNA Covid-19 vaccine than subjects vaccinated without history of COVID-19 infection. [8–11] *Krammer et al.* reported an antibody titer 10 to 45 times higher in vaccinees with previous immunity than seronegative participants after one shot of vaccine and at least 6 times higher antibody titers than seronegative participants after the second vaccine dose. [8] These results were confirmed by *Manisty et al.* who found that 19–29 days after one dose of BNT162b2 mRNA vaccine in 51 health care workers, subjects with previous immunity (n = 24) had an anti-spike IgG level>140 fold from peak pre-vaccine levels and a level significantly higher than those found in infection-naïve participants. Anti-spike antibody titres post vaccine in these infection-naïve individuals are similar to titres in individuals who have had a previous COVID-19 infection. [9] An investigation into the immunogenicity 21 days after one dose of BNT162b2 mRNA vaccine among 514 Israeli healthcare showed that immunogenicity was similar by ethnicity and sex, decreased with age. But participants with prior COVID-19 infection had antibody titres one magnitude order higher than naïve individuals regardless of the presence of detectable IgG antibodies pre-vaccination. [10] In addition a single BNT162b2 vaccine dose induces a significantly stronger T-cell responses to spike peptides and a significantly higher virus neutralization titers in individuals with previous virus exposure compared to infection-naive individuals. [11].

In the original paper, incidence of local side effects were similar between the first and the second dose while the second dose induced more adverse systemic reactions.[4] A recent study also

report that systemic symptoms were higher after the second dose of BNT162b2 mRNA vaccine especially vomiting, diarrhea, fatigue, muscle and joint pain. [12]

We hypothesize that the first dose of vaccine correspond to a second dose in subjects with prior COVID-19 infection with a higher humoral and T-cell response which may lead to a higher post vaccine reactogenicity. However further studies are needed to explore if reactogenicity post vaccine is related to the intensity of post vaccination humoral and cellular response.

Indeed, the main limit of our study is the small number of subjects with a history of previous SARS-CoV-2 infection and the absence of post vaccination serology. However groups were comparable for age and sex and the design of matched controls study improves the validity of our results.

5. Conclusion

Our study confirms a higher risk of short term side effects in patients with documented preexisting SARS-CoV-2 disease but with a good overall tolerance of BNT162b2 mRNA Covid-19 vaccine. These data are reassuring and should encourage confidence in the vaccination of this population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.06.054.

References

[1] https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-chiffres-cles-et-evolution-de-la-covid-19-en-france-et-dans-le-monde
[2] https://www.has-sante.fr/upload/docs/application/pdf/2021-03/actualisation_des_facteurs_de_risque_de_formes_graves_de_la_covid-19_et_des_reco_sur_la_strategie_de_priorisation_des_popula.pdf
[3] https://www.has-sante.fr/upload/docs/application/pdf/2021-02/strategie_de_vaccination_contre_le_sars-cov-2___vaccination_des_personnes_ayant_un_antecedent_de_covid-19_-_synthese.pdf
[4] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;31(383):2603–15. https://doi.org/10.1056/NEJMoa2034577.
[5] Baden LR, Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;4(384):403–16. https://doi.org/10.1056/NEJMoa2035389.
[6] https://www.fda.gov/media/73679/download
[7] https://ansm.sante.fr/uploads/2021/03/19/20210319-covid-19-vaccins-pfizer-comirnaty-9.pdf
[8] Krammer F, Srivastava K, Alshammary H, Amoako AA, Awawda MH, Beach KF, et al. Antibody Responses in Seropositive Persons after a Single Dose of SARS-CoV-2 mRNA Vaccine. N Engl J Med. 2021 Mar 10. https://doi.org/10.1056/NEJMc2101667.
[9] Manisty C, Otter AD, Treibel TA, McKnight Á, Altmann DM, Brooks T, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. Lancet 2021;20(397):1057–8.
[10] Abu Jabal K, Ben-Amram H, Beiruti K, Batheesh Y, Sussan C, Zarka S, et al. Impact of age, ethnicity, sex and prior infection status on immunogenicity following a single dose of the BNT162b2 mRNA COVID-19 vaccine: real-world evidence from healthcare workers, Israel, December 2020 to January 2021. Euro Surveill. 2021;26:2100096.
[11] Prendecki M, Clarke C, Brown J, Cox A, Gleeson S, Guckian M, et al. Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine. Lancet 2021;27(397):1178–81.
[12] Shaw RH, Stuart A, Greenland M, Liu X, Van-Tam JSN, Snape MD; Com-COV Study Group.Shaw RH, et al. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. Lancet. 2021 12:S0140-6736:01115-6.